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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,244	04/11/2000	ANDREAS STRAUSS	P64075USO	7733

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JACOBSON HOLMAN PLLC
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WASHINGTON, DC 20004

EXAMINER

HINES, JANA A

ART UNIT	PAPER NUMBER
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1645

MAIL DATE	DELIVERY MODE
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02/04/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/424,244

Applicant(s)

STRAUSS ET AL.

Examiner

Ja-Na Hines

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15-24 and 26-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15-24 and 26-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.1141.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 9, 2007 has been entered.

Amendment Entry

2. The amendment filed October 9, 2007 has been entered. Claims 1-14 and 25 have been cancelled. Claims 15-17, 20-21, and 23 have been amended. Claims 15-25 and 26-29 are under consideration in this office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments and arguments:

- a) The objection to claims 16, 17, 19 and 20;
- b) The rejection of claims 16, 18-25 and 26-29 under 35 U.S.C. 112, second paragraph;

Response to Arguments

4. Applicant's arguments filed October 9, 2007 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention..

5. Claims 15 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 15 recites that the active substances that affect the covalent bonding of polypeptides to the surface of Gram-positive bacteria are identified; however it is unclear what steps are taken in order to identify to substances. Therefore appropriate clarification is required to overcome the rejection.

b) Claim 17 recites the limitation "the bacteria cell wall" in the claim. There is insufficient antecedent basis for the limitation in the claim. Therefore despite applicants amendments to the claim, appropriate clarification is required to overcome the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 15-16, 20, 24, 26 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Samuelson (J. Bact., 1995, Vol. 177(6): 1470-1476).

The claims are drawn to a method for identifying active substances which affect the covalent bonding of polypeptides to the surface of Gram-positive bacteria, comprising the following steps: a) providing a sample of Gram-positive bacteria which contain or produce at least one enzymatic reporter substances which is or can become covalently bonded to the surface of the Gram-positive bacteria, said at least one reporter substance having a different enzymatic activity when not covalently bonded to the surface of the Gram-positive bacteria from that exhibited when it is covalently bonded to the surface of the Gram-positive bacteria; b) contacting the sample with a possible active substance; c) assaying the enzymatic activity of the reporter substance of the Gram-positive bacteria of the correlating the enzymatic activity of the reporter substance to a capability of the active substance to affect the covalent bonding of polypeptides to the surface of gram-positive bacteria to thereby identify the active substances that affect the covalent bonding of polypeptides to the surface of gram-positive bacteria. The dependent claims are drawn to the assaying of enzymatic activity, the hybrid polypeptide, the linker peptide, the gram-positive bacteria, and the reporter substances.

Samuelson (J. Bact., 1995) teaches cell surface display of recombinant proteins on *Staphylococcus carnosus*. Surface display of heterologous proteins on bacterial cells

is an important objective for many applications in microbiology and molecular biology (page 1470). The use of enzyme-coated bacteria as novel biocatalyst has been envisioned because enzymes with retained activity have been surface displayed on *E. coli* cells (page 1470). Investigations with gram-positive bacteria for cell surface display of has been initiated (page 1470). The surface receptors of gram positive bacteria seem to be more permissive for the insertion of extended sequences of foreign proteins than do the different gram-negative systems (page 1470). Gram-positive bacteria have the additional advantage of being more rigid because of the thicker cell wall, thus making it possible to use the intact bacteria for separation purposes (page 1470). A 198 amino acid region, designated ABP (albumin binding protein) was expressed adjacent to the cell wall to increase accessibility to the surface-displayed target peptides (page 1471).

The Materials and Methods section teaches enzymatic assay for the detection of recombinant surface displayed receptors (page 1471) and immunofluorescence assay for detection of peptides on the cell surface (page 1472). The method teaches contacting the sample and using a fluorescence activated cell sorter to analysis the bacteria (page 1472). The colorimetric assay for detection used strep avidin-alkaline phosphatase to detect a color change (page 1473). Recombinant and wild-type *S. carnosus* cells were grown and subjected to the enzymatic assay, performed in an ELISA plate format, wherein a positive color response was found for the cultivation harboring plasmids (page 1473). See Figure 3 which compares the wild type to the cultivations harboring plasmids. This demonstrates that hybrid receptors with serum albumin binding capacity were accessible on the cell surface (page 1474). For cell

surface binding, anchoring regions were investigated (page 1475). There is a charged repetitive region postulated to interact with the peptidoglycan cell wall and a region common for gram-positive cell surface bound receptors containing an LPXTGX motif, a C-terminal hydrophobic region and a charged tail (page 1475). It has been demonstrated that all three regions are required for cell surface anchoring and that the cell sorting is accompanied by proteolytic cleavage at the C-terminus and covalent linking of the surface receptor to the cell wall (page 1475). Samuelson et al., teach identifying the active substances that affect the covalent bonding of polypeptides to the surface of gram-positive bacteria.

Finally, flow cytometry was successfully employed and a fluorescence-labeled secondary antibody and a primary antibody reactive with the ABP region of the hybrid receptors could be used to stain the cells (page 1475).

Therefore, Samuelson (J. Bact., 1995) teaches a method for identifying active substances on the surface of gram-positive bacteria comprising: provision step; a contact step, an assaying step, a correlation step and inherently identifying the active substances that affect the covalent bonding of polypeptides to the surface of gram-positive bacteria.

Response to Arguments

7. Applicants' assert that Samuelson does not teach a method for identifying active substances that affect the covalent bonding of polypeptides to the surface of the gram-positive bacteria. In response to applicant's arguments, it is noted that Samuelson et al.,

teach identifying active substances such as albumin because albumin affects the covalent bonding of polypeptides to the surface of gram-positive bacteria; therefore contrary to applicants assertions, Samuelson et al., teach all the limitations of the rejected claims.

Applicants' assert that the teachings of Samuelson et al., do not specifically recite identifying the active substances that affect the covalent bonding of polypeptides to the surface of gram-positive bacteria. However, it is noted that the that the interpretive clause does not recite any additional active method steps but rather states a conclusion of the results of those steps. Therefore the teachings of Samuelson et al., meet the limitations of the claims. Therefore applicants arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 18-19, 21, 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Samuelson J. Bact., 1995. Vol. 177(6): 1470-1476) in view of Schneewind (Science, 1995. Vol. 268:103-105).

The claims are drawn to a method for identifying active substances which affect the covalent bonding of polypeptides to the surface of Gram-positive bacteria,

comprising the following steps: a) providing a sample of Gram-positive bacteria which contain or produce at least one enzymatic reporter substances which is or can become covalently bonded to the surface of the Gram-positive bacteria, said at least one reporter substance having a different enzymatic activity when not covalently bonded to the surface of the Gram-positive bacteria from that exhibited when it is covalently bonded to the surface of the Gram-positive bacteria; b) contacting the sample with a possible active substance; c) assaying the enzymatic activity of the reporter substance of the Gram-positive bacteria of the correlating the enzymatic activity of the reporter substance to a capability of the active substance to affect the covalent bonding of polypeptides to the surface of gram-positive bacteria to thereby identify the active substances that affect the covalent bonding of polypeptides to the surface of gram-positive bacteria. The dependent claims are drawn to the interpeptide bridges, the pathogenicity factors, the hybrid polypeptide, the expression of lyostaphin immunity factor and the reporter substances.

Samuelson (J. Bact., 1995) has been discussed however, Samuelson et al., (J. Bact., 1995) do not teach the cell wall structure and hybrids polypeptide succession.

Schneewind et al., (Science, 1995) teach structure of the cell wall anchor of surface proteins in *Staphylococcus aureus*. Schneewind et al., teach any surface proteins are anchored to the cell wall of gram-positive bacteria and are involved in the pathogenesis of these organisms (abstract). A hybrid molecule was designed and when expressed is anchored to the cell wall and can be released by controlled enzymatic digestion (abstract). Schneewind et al., teach a combination of molecular biology and

mass spectroscopy techniques, the structure of the cell wall anchor of surface proteins was revealed (abstract). After cleavage of surface proteins between threonine and glycine of the conserved LPXTG motif, the carboxyl of threonine is amide linked to the free amino group of the pentaglycine cross bridge in the staphylococcal cell wall (abstract). The N-terminal immunoglobulin-binding domains of protein A are displayed on the cell surface, whereas the C-terminal end is anchored to the bacterial cell wall (page 103). Schneewind et al., teach this ability to anchor to the cell wall requires a 35 residue sorting signal that is located at the predicted C-terminus of protein A and consists of an LPXTG motif, followed by a C-terminal hydrophobic domain and a tail of mostly positively charged residues (page 103). Cell wall anchored molecules of gram positive bacteria have similar topologies in that the N-terminal domain is displayed on the cell surface, whereas the C-terminal anchor structure is buried in the thick peptidoglycan layer (page 103). The pentaglycine peptide, lysostaphin cleaves randomly between any of the four glycyl-glycine peptide bonds (page 105). Schneewind et al., teach the lysostaphin cleavage occurred between the third and fourth glycine of the pentaglycine cross bridge, selectivity which could be the result of the steric hindrance imposed by the anchored protein and the linked cell wall peptide (page 105). Surface proteins are exported by a means of an N-terminal signal/leader sequence (page 105), See figure 4A and 4B. Schneewind et al., teach the release of peptidoglycan fragments with linked surface proteins in gram-positive bacteria may be caused by physiological turnover and the enzyme responsible may represent a novel target for antibacterial therapy (page 105).

Therefore, it would have been obvious at the time of applicants invention to modify the method of Samuelson (J. Bact., 1995) with polypeptides which effect the cell wall, pathogenicity, the use linker peptides and teach cell wall exchange as taught by Schneewind (Science, 1995), because Schneewind (Science, 1995) teaches that such modification are drawn to the structure of the cell wall anchor of surface proteins and designed an expressed hybrid molecule requires no more than routine skill. One of skill in the art would have been motivated to make such modifications because Schneewind teaches hybrid molecule can be released by controlled enzymatic activity. Furthermore no more than routine skill would have been required to incorporate such modifications when the art teaches novel targets for antibacterial therapy found by the release of peptidoglycan in gram-positive bacteria may be caused by physiological turnover and the responsible enzyme.

Response to Arguments

9. Applicants' argue that neither Samuelson et al., nor Schneewind et al., teach alone or in combination a method for identifying active substances which affect the covalent bonding of polypeptides to the surface of gram positive bacteria comprising a provision step; a contact step; an assaying step, and a correlation step to thereby identify the active substances that affect the covalent bonding of polypeptides to the surface of gram-positive bacteria. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce

the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been prima facie obvious at the time of applicants invention to modify the method of Samuelson (J. Bact., 1995) with polypeptides which effect the cell wall, pathogenicity, using linker peptides and teaching cell wall exchange as taught by Schneewind (Science, 1995), because Schneewind (Science, 1995) teach that such modification are drawn to the structure of the cell wall anchor of surface proteins and designed an expressed hybrid molecule requires no more than routine skill. Therefore applicants' argument is not persuasive and the rejection is maintained.

Applicants argue that an advantageous result occurred, there this result establishes patentability over the art. However any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (differences in sedative and anticholinergic effects between prior art and claimed antidepressants were not unexpected). Thus a difference or advantageous result is not sufficient to overcome the obviousness rejection. Furthermore, mere allegations of unexpected results are not sufficient to overcome the rejection, evidence must show unexpected results. Just as a greater than additive effect is not sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or

unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991). Therefore applicants arguments are not persuasive and the rejection is maintained.

10. Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Samuelson J. Bact., 1995. Vol. 177(6): 1470-1476) in view of Schneewind (Science, 1995. Vol. 268:103-105) in further view of Strauss et al. (Mol. Microbio. 1996. Vol. 21(3): 491-500).

The claims are drawn to a method for identifying active substances which affect the covalent bonding of polypeptides to the surface of Gram-positive bacteria, comprising the following steps: a) providing a sample of Gram-positive bacteria which contain or produce at least one enzymatic reporter substances which is or can become covalently bonded to the surface of the Gram-positive bacteria, said at least one reporter substance having a different enzymatic activity when not covalently bonded to the surface of the Gram-positive bacteria from that exhibited when it is covalently bonded to the surface of the Gram-positive bacteria; b) contacting the sample with a possible active substance; c) assaying the enzymatic activity of the reporter substance of the Gram-positive bacteria of the correlating the enzymatic activity of the reporter substance to a capability of the active substance to affect the covalent bonding of

polypeptides to the surface of gram-positive bacteria to thereby identify the active substances that affect the covalent bonding of polypeptides to the surface of gram-positive bacteria. The dependant claims are drawn to the hybrid polypeptide, and a proenzyme.

Samuelson (J. Bact., 1995) and Schneewind have been discussed however, neither does not teach the enzyme being a proenzyme.

Strauss et al., teaches *in vivo* immobilization of enzymatically active polypeptides on the cell surface of *Staphylococcus carnosus*. Many surface proteins of gram-positive bacteria are covalently anchored to the cell wall by ubiquitous mechanisms, involving a specific, C-terminal sorting signal (abstract). To achieve cell wall immobilization of a normally secreted enzyme *in vivo*, the authors constructed a hybrid protein consisting of *Staphylococcus hyicus* lipase and *S. aureus* fibronectin binding protein B (abstract). The lipase is a pre-proenzyme (page 492). Expression of the hybrid protein in *S. carnosus* resulted in efficient cell-wall anchoring of enzymatically active lipases (abstract). The cell wall lipase retained more than 80% of the specific activity as compared to unmodified lipase (abstract). When the lipase was replaced by another enzyme, the resulting hybrid was also efficiently anchored in an active conformation to the cell wall of the bacteria (abstract). The results demonstrate that it is possible to immobilize normally soluble enzymes on the cell wall of *S. carnosus*, without radically altering their catalytic activity, by fusing them to a cell wall immobilization unit, consisting of a suitable cell wall spanning region and a standard cell wall sorting signal (abstract).

Therefore, it would have been obvious at the time of applicants' invention to modify the method of Samuelson (J. Bact., 1995) and Schneewind because Strauss et al., teach that proenzymes are usable with the well known method of identifying substances which affect the covalent bonding of polypeptides to the surface of gram-positive bacteria. One of skill in the art would have been motivated to make such modifications because Strauss et al., teach cell wall immobilization and the construction of a hybrid protein, just as taught by Samuelson (J. Bact., 1995) and Schneewind; therefore no more than routine skill would have been required to use an alternative functionally equivalent hybrid in a well known method of identification. Furthermore, no more than routine skill would have been required to use of proenzyme and determine the change in enzymatic activity when the art teaches that changes in enzymatic activity can occur without radically altering their catalytic activity thereby making them useful in said methods of identification.

Response to Arguments

11. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of skill in the

art would have been motivated to make modify the method of Samuelson (J. Bact., 1995) and Schneewind because Strauss et al., teach cell wall immobilization and the construction of a hybrid protein. Therefore no more than routine skill would have been required to use an alternative and functionally equivalent hybrid in a well known method of identification. Moreover, no more than routine skill would have been required to use of proenzyme and determine the change in enzymatic activity when the Samuelson (J. Bact., 1995) Schneewind and Strauss teach that changes in enzymatic activity can occur without radically altering their catalytic activity thereby making them useful in said methods of identification.

***New Grounds of Objection
Claim Objections***

12. Claim 29 is objected to because of the following informalities: The claim recites "int hat". Appropriate correction is required.

Conclusion

13. No claims allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.


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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
December 19, 2007


MARK NAVARRO
PRIMARY EXAMINER